SEDATION SOLUTIONS

Ketofol 111: Risky or Revolutionary

Abstract

This article focuses on propofol, a non-barbiturate intravenous anaesthetic agent with a quick onset and recovery after administration. Propofol, because of its unique pharmacokinetics and pharmacodynamics, has become a popular agent for use during procedural sedation and analgesia (PSA). Its use is however not without controversy. There is currently a worldwide debate on who should be allowed to administer propofol for PSA outside the operating theater. Some anaesthetists feel that only they should be allowed to administer this drug. Non-anaesthetists on the other hand feel that they can also administer propofol safely. According to twenty- one European countries who are members of the European National Societies of Anaesthesia, “non-anaesthetists should not be allowed to administer propofol for PSA: a consensus statement”. This is a retraction of a previous endorsement of the use of propofol by non-anaesthetists. They now feel that ”propofol belongs to the anesthetists”. This view is however not supported by all anaesthetic societies.

Propofol’s sedative and amnestic properties make it ideal for brief, non painful procedures. The drug has significant antiemetic properties, with a very low incidence of nausea and vomiting. However, desaturation with propofol may occur with rapid administration.

Readers are reminded that a full list of references will be published at the end of our series on ketofol.

Introduction

Propofol

Propofol was approved in 1989 by the FDA (USA) for use by anaesthetists for general anaesthesia. Since then non-anaesthetists have made numerous attempts to convince the FDA that they can also administer propofol safely. There are in fact quite a number of evidence-based studies available, done by non-anaesthetists, supporting their position. The FDA now accepts that “the doctor who administers propofol must have the skills and the knowledge with the attention strictly focussed on the act”. If one looks at the comments of the FDA then it seems they support the use of propofol by dedicated sedation practitioners during PSA; maybe not operator sedationists.

The use of propofol for PSA in the emergency department was first described in 1996. Today it is a very popular drug for PSA with increasing support for its use by emergency physicians for various procedures in adults and in children.

On account of its favourable pharmacokinetic profile propofol has become the induction agent of choice for general anesthesia and one of the preferred agents for PSA. The drug is a short-acting sedative hypnotic, with no analgesic action, with a half-life of 4 minutes in adults (children 9 minutes). It causes non-dissociative sedation, which simply means the more you give to a patient the deeper the patient will become. It is a phenol-derivative with the chemical name of 2,6-diisopropylphenol. It is a white oil-in-water emulsion of 10% soya bean oil, 2,25% glycerol and 1,2% purified egg phosphatide. It is important to note that only the reformulated original brand contains the purified egg phosphatide and EDTA, whereas generic brands contain egg lecithin and no EDTA[15].

All propofol preparations with the exception of the newly available fosfopropofol (Lusedra™) are lipid suspensions that contain egg lecithin/phosphatide and soy oil.

A strict aseptic technique is still advocated during use of propofol as the 0,005% EDTA may inhibit the growth of micro-organisms for up to 12 hours, but contamination remains a risk. It is slightly soluble in water, isotonic, with a pH of 7 - 8,5 and a pKa of 11. It can be given to patients with a predisposition

to, or suspected malignant hyperthermia, epilepsy, porphyria, and muscular diseases.

It is thought that propofol directly activates $GABA_A$ receptors and inhibits glutamate release[8]. The inhibition of glutamate is for us as sedation practitioners of interest as we sedate many patients suffering from depression and taking anti-depressant drugs. It is well known that patients with depression have excessive levels of glutamate in the blood. It looks like, and this is what we find in the clinical situation, that propofol is a safe drug to use in patients with depression.

Propofol produces general anaesthesia by facilitation of inhibitory neurotransmission mediated by GABA. With propofol administration during PSA all the levels of sedation displayed on the sedation continuum can be reached depending on the dose we administer e.g. minimal -, moderate -, deep sedation, and even general anaesthesia.
This is a spectrum of sedation that needs to be clearly understood by the sedation practitioner when using propofol for PSA. Propofol should be administered with great care and where possible titrated to response. With propofol the patient may be able to maintain a patent airway and respond purposefully and verbally. On the other side patients may quickly slip into deeper levels of sedation accompanied by a partial or complete loss of protective reflexes. The point on the continuum where the reflexes are lost is not known and does not correlate with patient responsiveness. Patient should therefor be carefully monitored for their level of consciousness during use of propofol for PSA.

The pharmacokinetics of propofol is best described by a three-compartment linear model with compartments representing the plasma, rapidly equilibrating tissues and slowly equilibrating tissues[8]. Following intravenous administration, rapid equilibration between the plasma and brain concentrations follow, where after plasma concentrations decline rapidly as a result of both distribution and metabolic clearance. It is extensively bound to plasma proteins, although the plasma level initially shows a steep decline as a result of both rapid distribution and high metabolic clearance. This translates in practice to a rapid

onset of action of about thirty seconds, and, following a bolus injection, the blood concentration declines rapidly[13]. Administration by infusion, however, produces an initial rapid increase in concentration, a rapid decline and then a slower rise to a steady state[23].

This observation of "slower infusion of the same bolus dose results in lower peak serum concentrations and reduced target organ effects" leads to a reduction in adverse events and suggests that target-controlled infusions (TCI) might be superior to bolus dosing[4,5,20]. During bolus dosing an adequate interval of 3-5 minutes must be allowed between dose adjustments in order to assess the possible clinical effects. This is extremely important in all patients but great care must be exercised in the elderly.

Hepatic extraction of propofol is high and clearance is dependent on liver blood flow[20]. Propofol has been shown to decrease cardiac output in a dose-dependent manner in humans, which in turn may dynamically influence propofol kinetics by reducing the rate of distribution to peripheral tissues and thereby contributing to a reduction in hepatic blood flow[19,20]. Coetzee et al proposed the clearance of propofol is concentration dependant, and that clearance of high doses is significantly slower when compared to lower doses[20]. Elimination is by hepatic conjugation to inactive glucuronide metabolites excreted by the kidneys.

Prolonged propofol use of more than 12 hours, which is probably non-existent during PSA, causes accumulation and slower recovery. Discontinuation of propofol infusion leads to a decrease of 50% of the serum drug level within 10 minutes, after which the excretion rate becomes more variable, based on the duration of therapy and total dose given. As predicted by the rapid decrease in serum drug levels, most patients are able to respond to verbal commands within 10 minutes. The sedation practitioner must take into account that other sedative/analgesic drugs may also be used, and they may contribute to a longer recovery time.

Infants have a larger volume of distribution and a greater metabolic clearance than older children. Consequently bolus doses to achieve clinical effect are higher in infants. Similarly, because the metabolic clearance is higher in

infants, continuous infusion rates are greater. Paediatric patients generally require bolus doses of up to 50% greater than those used for adults and maintenance infusion rates of 25-50% greater than those effective in adult patients[26]. It must be remembered by the sedation practitioner that with higher doses there may be a longer recovery period.

Propofol has amnestic properties, a short recovery time and direct anti-emetic effects[3]. Some clinicians believe propofol has amnestic properties only at doses of 3 – 5 mg/kg/hr. Similarly to benzodiazepines it is anxiolytic in doses that do not cause sedation[8].

The use of propofol can be limited by dose-dependent respiratory and cardiovascular depression and hypotension[31]. Its use is associated with a dose-dependent risk of respiratory depression. This risk is heightened with concomitant opioid use and other sedatives or rapid administration. This can be problematic for the sedation practitioner wishing to provide analgesia with opioids as propofol has no intrinsic analgesic properties. It is claimed that when we combine ketamine and propofol (ketofol) we need less propofol and then a lower incidence of respiratory-related adverse events, and we also provide analgesia. This will be discussed in the following article.

The major cardiovascular effect is hypotension with little or no change in heart rate and no appreciable decrease in cardiac output[13]. This can be a serious complication especially in the elderly during PSA. According to the FDA drug information pamphlet, apnoea lasting longer than 60 seconds has been observed in 12% of adult patients at general anaesthetic induction doses of 2 to 2,5mg/kg, doses we do not use during PSA. At such high doses it causes a decrease in minute ventilation which may be marked, depending on the rate of administration and concurrent use of other medications. It must be stressed that the doses mentioned are anaesthetic doses, and not the doses that we use for PSA.

Studies show that the recovery time with propofol is shorter compared to midazolam, but more or less equivalent to that of hypnomidate, and that patient satisfaction rates are higher [3,13]. The ability to use infusion techniques with propofol most likely also contributes to the consistency and reproducibility

of the quality of sedation. Add to that the ease of titration and the rapid return of wakefulness, and it is difficult to find reasons to omit propofol from a sedation regimen using advanced sedation techniques.

Propofol decreases cerebral oxygen consumption, cerebral metabolic rate, and intracranial pressure. Some clinicians feel one should use propofol with care in epileptic patients and that the drug should only be used in controlled epileptic patients. It is lipophilic and crosses the blood-brain barrier easily. It is also classified as an anti-oxidant with an anti-inflammatory action and is also known as a bronchodilator[8].

One of the most noticeable side effects of propofol is burning on injection. Several solutions are used to prevent this. One of the solutions used to reduce pain is the addition of lignocaine. Studies suggest that 1ml of a 2% lignocaine solution should be added to 20ml of propofol in the same syringe[57]. There are reports in the literature that the addition of lignocaine in quantities of more than 20mg of lignocaine in 200mg propofol results in instability of the solution which is associated with increases in globule sizes over time and a reduction in anaesthetic potency[57]. In study yet to be published Le Guen et al looked at the comparison of potency when different propofol formulations were used. They found that induction doses for general anaesthesia were similar when propofol formulations were mixed with lignocaine.
Some clinicians suggest that ketamine 0.2mg/kg, or tramadol 50mg can be mixed with propofol to prevent burning with intravenous administration of propofol.

It is reported that propofol administration can be associated with transient cognitive dysfunction, coughing, movement and pruritus.

Propofol infusion syndrome has been described in patients receiving propofol infusions in doses of more than 5mg/kg/hour for more than 48 hours[8]. It usually presents as a sudden-onset bradycardia that is resistant to treatment, and progressing to asystole, combined with a lipaemic plasma, hyperkalaemia, fatty liver enlargement, metabolic acidosis and rhabdomyolysis. In theory, it must be a risk in procedural sedation as well, but Crawford et al reported their experience of 100 000 propofol sedations and anaesthetics for children in a

paediatric hospital without one documented case of the propofol infusion syndrome[52].

It is now postulated that a mitochondrial defect may be a factor in the development of propofol infusion syndrome. If this is the case then all sedation practitioners must always monitor patients carefully whenever propofol is administered.

A history of hypersensitivity to egg and soy are listed as contraindications to the use of propofol. Propofol hypersensitivity reactions are uncommon. Newly available fosfopropofol may be used as an alternative.

Propofol is claimed to be the best of all sedative/hypnotic intravenous drugs for paediatric sedation. However, its narrow therapeutic window and the vulnerability of children to the sedative effects may lead quickly to unintended deep sedation and inadvertent loss of consciousness, with the loss of protective reflexes even after small dose increases[18].

The use of propofol for procedural sedation is not without risks and adverse events. These include apnoea, hypoxia, airway obstruction and cardiovascular events such as hypotension. However, these events are not unique to propofol and are well documented for other sedation agents. Sedation practitioners must however be trained to use propofol.

Propofol was compared to a combination of ketamine and propofol in sedation. The results of the trial showed that the end-tidal carbon dioxide values were lower in the propofol-ketamine group, with less effect on ventilation[31]. There were no differences in blood pressure, heart rate, oxygen saturation and number of adverse events between the two groups. There were no statistical differences in the time spent in recovery prior to discharge. The visual analogue pain scores though, were higher in the propofol only group. The postoperative mood scores were higher in the combination group. The amount of opioid used after discharge was lower in the combination group, attributed to the analgesic properties of ketamine[31].

Dosing scheme for propofol

Bolus dose	Titration interval	Onset of action	Repeat dose	Duration of action
0.5 mg/kg over 2-3 min	1 minute	30 – 60 seconds	0.25 mg/kg titrated to effect	4 – 5 minutes

The doses above are for healthy adult ASA 1 patients: with elderly patients the dose should be halved and titrated to effect. It must be remembered that a clinical effect will take longer in the elderly.

In children where we administer propofol as part of a sedation regimen we start at the same bolus doses, and titrate to effect.

Dosing scheme for propofol infusions for PSA

The administration of propofol using an infusion technique for PSA has become very popular for various reasons. It must be remembered that propofol must be titrated to clinical effect as we cannot always predict the outcome. Patients may slip inadvertently into deeper levels of sedation.

Intravenous infusion	Target controlled infusion
2–4 mg/kg/hour titrated to clinical effect	Effect site concentration 1-2 µg/ml: it is believed that the eyelid reflex will

	disappear at a TCI of 2.2 μg/ml
In elderly patients, start infusion at 1–2 mg/kg/hour and titrate to clinical effect	In elderly patients, recommended effect site concentration to commence with is 0.6-0.8 μg/ml

Conclusion

It is clear that propofol is a significant drug in the armamentarium of the sedation practitioner. The drug has many of the characteristics of an ideal sedative/hypnotic agent, and we discover more are more about this drug. Several different formulations of propofol are now being tested.

It remains a potent drug for PSA that should be used carefully. Patients must be monitored with utmost care. Sedation practitioners who administer this drug must be trained in the use of propofol.

More CPD articles will follow where the combination of propofol and ketamine will be discussed.

References

With the last CPD article in this series a full list of references will be provided.